5. (Amended) A synthetic nucleotide comprising a conserved portion in the nucleic acids of enteroviruses, said sequence being selected from the group consisting of:

SEQ ID NO: 9: TCCTCCGGCCCCTGAATGCGGCTAATC,

SEQ ID NO: 10: TGTCGTAACGSGCAASTCYGYRGCGGAACCGAC,

SEQ ID NO: 11: TACTTTGGGTGTCCGTGTTTCHTTTTAT,

SEQ ID NO: 12: CTTATAAGCAGACTCAACCCGGTGCTGATG,

SEQ ID NO: 13: TGGCATTCCAATATCACAATTAACAGTG,

SEQ ID NO: 14: CTCGGCACTATCGCAGGAGGGACCGGGAAT and

SEQ ID NO: 15: CCTACGCCACTACACAGCCTGGTCAGGTTG, and a degenerate sequence of any of SEQ ID Nos: 12-15,

Which specifically hybridizes to a sense strand of an enterovirus nucleic acid or a nucleic acid comprising the sense strand.

REMARKS

In the Office action mailed October 23, 2002, the specification is objected to due to an informality; claims 5 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite; claim 5 is rejected under 35 U.S.C. § 102(a) as being anticipated by Accession number AF136379 (June 2000); claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number Z78129 (August 1997); claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number U55870 (May 1996); claims 1-5 and 21-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kilpatrick (U.S. Patent No. 6,168,917: 102(e) dated July 9, 1999) in view of Accession numbers U22521 (January 1997), AF177911 (September 1999), AF136379 (June 2000), U55870 (May 1996),

and Z78129 (August 1997), and further in view of Accession number E30248 (from JP 1999346799, published December 1999).

In response, applicant has amended the specification to correct the noted informality, and has amended claims 1 and 5 to overcome the rejections.

Applicants respectfully submit that the present application relates to certain conserved portions in nucleic acids of known pathogenic enteroviruses, which were identified by the present application for the first time (see paragraph beginning on line 31 of page 2 of the specification). According to the present application, novel pairs of primers were designed in light of the conserved portions. The pairs of primers are utilized in this invention for detecting if any of various types of enteroviruses is present in a sample (see Example 1, pages 16-21, of the specification), Also, the present application provides synthetic nucleotide sequences according to those conserved portions among the genomes of enteroviruses. As illustrated in Example 1 of the present application, the synthetic nucleotide sequences used as probes specifically hybridized to the amplification products that were obtained using the pairs of primers of this invention. Furthermore, two synthetic nucleotide sequences (SEQ ID Nos: 12 and 13) were used to differentiate enterovirus type 71 and two other sequences (SEQ ID Nos: 14 and 15) were used to differentiate coxackievirus A16, see Example 2, page 21 of the present specification.

Even though the genome (or their part) of some enterovirus strains have been sequenced and published, the state of the art at the time this application was filed neither taught nor suggested the conserved portions that were identified in the present application for the first time. Therefore, a person skilled in the art would have no way to anticipate the conserved

portions, much less the pairs of primers of claim 1 and the synthetic nucleotide sequences (probes for confirmation and differentiation) of claim 5, both of which were first derived from the conserved portions among various enteroviruses according to the present application.

I. Response to the Objection to Claims 5 and 23 Under 35 U.S.C. § 112, Second Paragraph.

1. In light of the Office action's reference to the word "capable" and the applicants' intent to claim the function of *"specifically* hybridizing" as a property of the claimed *probes,* the term "is capable of" was deleted from claim 5, and claim 5 was amended to reflect the applicant's intent.

These probes relate to the primers in claim 1 that are employed to amplify a sequence of a conserved portion in enteroviruses (see Example 1.5. Hybridization analysis, page 19, and Example 2.2. Hybridization assay, page 21).

The probes in Claim 5 are used to hybridize with the amplification products that were obtained using the pairs of primers of this invention.

Applicants have amended Claim 5 to overcome this objection.

2. As described in the specification, the phrase "corresponding to the sense strand" means the nucleotide sequences comprising the sense strands.

On page 13, lines 12-15, the specification specifically states, "Therefore, the present application further provides the synthetic nucleotide sequences capable of specifically hybridizing to a sense strand of an enterovirus nucleic acid or a nucleic acid corresponding to the sense strand *(such as the product of an amplification reaction using the sense strand as the template).*"

Since the enterovirus is a single strand of positive-sense RNA, the claimed probes in Claim 5 are antisense probes that specifically hybridize to the nucleotide sequences comprising the sense strands.

Applicants have amended Claim 5 to overcome this objection.

3. Claim 23 clearly claims an additional feature, i.e., "at least one synthetic nucleotide sequence according to claim 5," over the features reflected in Claims 22 and 21. Because of the dependence of Claim 23 on Claim 22, the features claimed in Claim 23 including: "more than one pair of oligonucleotide primers according to claim 1, and at least one synthetic nucleotide sequence according to claim 5, where the pairs of oligonucleotide primers are limited as defined in claim 21."

No limitations or restrictions in Claims 1, 5, 21, or 22 preclude any of the synthetic nucleotide sequences in Claim 5 being present in the kit claimed in Claim 23. Applicant therefore respectfully disagrees with the assertion to the contrary in the Office action.

II. Response to the Rejection of Claim 5 Under 35 U.S.C. § 102.

Claim 5 is rejected under 35 U.S.C. § 102(a) as being anticipated by Accession number AF136379 (June 2000), and is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession numbers Z78129 (August 1997) and U55870 (May 1996).

Even though the genome (or their part) of some enterovirus strains have been sequenced and published, the state of the art at the time this application was filed neither taught nor suggested the conserved portions that were identified in the present application for the first time. Therefore, a person skilled in the art would have no way to anticipate the conserved

portions, much less the synthetic nucleotide sequences (probes for confirmation and differentiation) of claim 5, which were first derived from the conserved portions among various enteroviruses according to the present application.

III. Response to the Rejection of Claims 1-5 and 21-26 Under 35 U.S.C. § 103.

With regard to the substantive issues, Claims 1-5 and 21-26 were rejected under 35 U.S.C. § 103 as being unpatentable over Kilpatrick. Applicants set forth below the distinct differences between the present application and the cited patent.

The present application relates to certain conserved portions in the nucleic acids of known pathogenic enteroviruses, which were identified by the present invention for the first time (see the paragraph across pages 2 and 3 of the specification). According to the present application, novel pairs of primers were designed in light of the conserved portions. The pairs of primers are utilized in this invention for detecting if any of various types of enteroviruses is present in a sample (see Example 1, pages 16-21 of the specification). Also, the present invention provides synthetic nucleotide sequences according to those conserved portions among the genomes of enteroviruses. As illustrated in Example 1 of the present application, the synthetic nucleotide sequences used as proves specifically hybridized to the amplification products were obtained using the pairs of primers of this invention. Furthermore, two synthetic nucleotide sequences (SEQ ID Nos: 12 and 13) were used to differentiate enterovirus type 71 and two other sequences (SEQ ID Nos: 14 and 15) wee used to differentiate coxackievirus A16, see Example 2, page 21 of the present specification).

Since Kilpatrick was not aware of the existence of the conserved portions among

enteroviruses according to the present invention, no evidence indicates that a person skilled in the art could devise the primers of Claim 1 based on the conserved portions, much less the kits of Claims 21-26.

Accordingly, the subject matter of Claims 1-5 and 21-26 was invented based on the knowledge that Kilpatrick's patent neither taught nor suggested. Claims 1-5 and 21-26 are not obvious to a person skilled in the art in light of Kilpatrick's patent.

As required by 37 C.F.R. § 1.121, applicants have provided a separate marked-up version of the amended claims showing the changes relative to the previous version of those claims (attached).

The above amendments and remarks are believed to address fully the Examiner's rejections, and place the application in condition for allowance. A prompt indication of the same respectfully is requested. The Examiner is encouraged to telephone the undersigned if any issues remain that may be resolved by a telephonic interview.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on January 15, 2003.

Charles H. DeVoe
Date of Signature: January 15, 2003

23581
PATENT TRADEMARK OFFICE

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the paragraph beginning on line 17 of page 6, as follows.

(Amended) Figure 1 is a schematic representation showing a portion of cDNA sequence (SEQ ID NO 16) corresponding to the genome of enterovirus type 71, where the cDNA sequence with the Accession No. U22521 was obtained from the database GenBank. The sequences in the boxes correspond to the primers and probes of the present application that are identified with their codes designated by the inventors.

In the Claims:

Please amend claims 1 and 5, as follows.

1. (Amended) A pair of oligonucleotide primers for use in detecting the presence or absence of an enterovirus in a sample, wherein a first primer of said pair comprises a sequence of any of:

SEQ ID NO: 1: TTGTRCGCCTGTTTTA,

SEQ ID NO: 2: CAAGCACTTCTGTHHCCCCGG,

SEQ ID NO: 3: TACTTCGAGAARCCYAGTA,

SEQ ID NO: 4: AAGAGYCTATTGAGCTA, or

SEQ ID NO: 5: GGITGGTRSTGGAARTTICC, or a degenerate sequence of SEQ ID No: 5;

and

a second primer of said pair comprises a sequence of any of:

SEQ ID NO: 6: CACYGGATGGCCAATCCAA,

SEQ ID NO: 7: ATTGTCACCATAAGCAGCCA, or

SEQ ID NO: 8: ARRTTIATCCAYTGRTGIGG, or a degenerate sequence of SEQ ID No: 8,

where the first primer and the second primer can be employed to amplify a sequence of a conserved portion in the nucleic acids of enteroviruses,

provided that the second primer comprises the sequence of SEQ ID NO: 8 or a degenerate sequence [there]of SEQ ID NO: 8 when the first primer comprises the sequence of SEQ ID NO: 5 or a degenerate sequence [there]of SEQ ID NO: 5.

5. (Amended) A synthetic nucleotide comprising a conserved portion in the nucleic acids of enteroviruses, said sequence being[any] selected from the group consisting of:

SEQ ID NO: 9: TCCTCCGGCCCCTGAATGCGGCTAATC,

SEQ ID NO: 10: TGTCGTAACGSGCAASTCYGYRGCGGAACCGAC,

SEQ ID NO: 11: TACTTTGGGTGTCCGTGTTTCHTTTTAT,

SEQ ID NO: 12: CTTATAAGCAGACTCAACCCGGTGCTGATG,

SEQ ID NO: 13: TGGCATTCCAATATCACAATTAACAGTG,

SEQ ID NO: 14: CTCGGCACTATCGCAGGAGGGACCGGGAAT and

SEQ ID NO: 15: CCTACGCCACTACACAGCCTGGTCAGGTTG, and a degenerate sequence of any of SEQ ID Nos: 12-15,

Which [is capable of]specifically [hybridizing]hybridizes to a sense strand of an enterovirus nucleic acid or a nucleic acid comprising[corresponding to] the sense strand.